Memo

To: File

From: E Gross Bermudez

CC: F. Miller, Vice President for Research

        R. Conolly, Senior Investigator

        A. Jarabek, US EPA Visiting Scientist

Date: June 15, 2004

Re: HCHO studies – Tumor Incidence

The purpose of this memorandum is to document the data from the various formaldehyde publications sponsored by or conducted at the CIIT Centers for Health Research (CIIT) and to resolve some data discrepancies and arrive at a final data set that can be used for modeling. This memo includes the total CIIT formaldehyde data set (combined Kerns, Monticello, Everitt) that is available on CD and the information on CIIT's use of the NTP control data base.

Kerns Study (Table 4-7 in 1999 CIIT report)

Updating the data summary for the Kerns et al. (1983) study in the 1999 CIIT report on Page 4-20 to reflect all animals for which there are nasal slides and a consensus of pathology diagnoses, the tumor summary is as follows: 0 animals out of 237 animals at 0 ppm; 0 out of 239 at 2 ppm; 2 (1Male, 1Female) animals out of 235 at 6 ppm; 83 (31M, 52F) animals out of 225 at 15 ppm.

Concentration	Total Examined	SCC Tumors	No Tumors
0	237	0	237
2	239	0	239
6	235	2	233
15	225	83	142

The total examined at all concentrations except the 6 ppm level was increased. These changes correct for what may have been misinterpretations of the incidence numbers presented in the original Kerns report (number of

animals on study vs. number of animals examined) and/or limitations in data presented in the Kerns et al. (1983) publication.

Monticello Study (Table 7-3 in 1999 CIIT Report)

The following table replaces Table 7-3 in the 1999 CIIT report on Page 7-10 for the data summary of the Monticello et al. (1996) study. The only changes made are for 2 ppm rats where the number of noses examined was 96 not 90. The 90 was a typographical error as an additional 18 animals were examined by Jeff Everitt not 24.

	Formaldehyde concentration (ppm)					
	0.0	0.7	2.0	6.01	9.93	14.94
Monticello et al. (1996)						
Number SCC	0	0	0	1	20	69
Number examined	90	90	96	90	90	147
Additional animals – CIIT (1999)						
Number SCC	0	0	0	0	2	10
Number examined	14	17	18	18	13	14
Total number of SCC	0	0	0	1	22	79
Total number of animals examined	104	107	114	108	103	161

Summary Information

The following table provides a summary of the data for the two studies sponsored or performed by CIIT (Kerns et al., 1983 and Monticello et al. , 1996).

Summary Table for Kerns and Monticello Studies Combined

Concentration	Total Examined	SCC Tumors	No Tumors
0	104	0	104
.7	107	0	107
2	114	0	114
6	108	1	107
10	103	22	81
15	161	79	82

Note added by Rayi 1-30-16:
Conolly (2003) explains that tissues from an additional 94 rats from the Monticello study were available that had not been previously examined. These tissues were from the 12, 18 and 24-month time points and were distributed approximately evenly across the six exposure concentrations. The squamous cell carcinoma (SCC) data from these 94 rats were combined with the Kerns et al. and Monticello et al. SCC data in the CIIT and the individual animal data are reported in the Appendix in Conolly (2003). EPA's analysis used the combined data from Conolly (2003). (Note: the combination was carried out because SCC incidence and survival rates appeared to be similar).

For control animals, 3,866 males and 3,818 females were used from the NTP historical data base. CIIT classified 13 of 15 NTP classified nasal tumors as nasal SCCs (based on examination by Kevin T. Morgan). The Kerns study examined 237 control animals and the Monticello study, 104 (90 originally and 14 added by Jeff Everitt). No control SCCs were reported in the Kerns or Monticello studies. The total of 8025 for controls and the total examined at other concentrations also includes animals that were very young (prior to the first tumor diagnosis), unscheduled animals and animals that were held for examination up to 6 months beyond the 24-month bioassay. The number of control animals from the CIIT Dataset (available on CD) represents animals for which slides of the nasal cavity are available and may include animals not reported in the Kerns or Monticello published incidence tables. This confirms 13 tumors out of 8025 control animals examined.

Because the biologically-based dose-response (BBDR) model used all of these data, including both bioassays, the additional evaluations by Dr. Jeff Everitt, and the animals that were held post-exposure, any other type of dose-response modeling approaches should attempt to address comparable data sets. As stated above it should be noted that some animals at all concentrations were examined at a very young age (Monticello and Kerns studies, early time points) and this needs to be taken into consideration when using these data.

These data are summarized in the following table.

Summary Table for Data Used in Biologically-Based Dose Response (BBDR) Model Developed by the CIIT Centers for Health Research (Conolly et al., 2003)

Concentration	Total Examined	SCC Tumors	No Tumors
0	8025	13	8012
0.7	107	0	107
2.0	353	0	353
6.0	343	3	340
10.0	103	22	81
15	386	162	224

Conolly Modeling (Appendix Table 1 in 2003 Toxicological Sciences paper)

The time of death due to tumors of the thirteen (13) tumors from the control NTP data are listed in the following table. These dates were used in the BBDR model so that the dates essentially replace the "N/A" in the first column listed for the control animals in Appendix Table 1 of Conolly et al., (2003). The death dates of the survivor animals were not available and therefore are all estimated and entered as 104.4 weeks for these animals. This assumption was felt justified because of it being such a large data set that the loss of a few animals at other times during their lifetime would not unduly affect their estimate of lifetime nasal SCC probability.

Weeks from start of study	Number of rats with tumors	Cumulative probability
50	1	0.0001
85	1	0.0003
87.6	1	0.0004
91	1	0.0005
91.9	1	0.0007
93.7	1	0.0008
94.9	1	0.0009
96.6	1	0.0010
96.9	1	0.0012
97.6	1	0.0013
98.1	1	0.0014
102.3	1	0.0016
104.4	1	0.0017